TITLE: Breast cancer treatment patterns by age and time since last pregnancy in the Carolina Breast Cancer Study-Phase III

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ABSTRACT (Limit: 250 words; current: 248 words)

Purpose: To describe breast cancer treatment patterns among premenopausal women by age and time since last pregnancy.

Methods: Data were analyzed from 1,179 women diagnosed with premenopausal breast cancer in the Carolina Breast Cancer Study. Of these, 160 had a recent pregnancy (within 5 years of cancer diagnosis). Relative frequency differences (RFDs) and 95% confidence intervals (CIs) were used to compare cancer stage, treatment modality received, treatment initiation delay (>30 days), and prolonged treatment duration (>2 to >8 months depending on the treatment received) by age and recency of pregnancy.

Results: Recently postpartum women were significantly more likely to have stage III disease [RFD (95% CI): 12.2% (3.6%, 20.8%)] and to receive more aggressive treatment compared to nulliparous women. After adjustment for age, race and standard clinical tumor characteristics, recently postpartum women were significantly less likely to have delayed treatment initiation [RFD (95% CI): -11.2% (-21.4%, -1.0%)] and prolonged treatment duration [RFD (95% CI): -17.5% (-28.0%, -7.1%)], and were more likely to have mastectomy [RFD (95% CI): 14.9% (4.8%, 25.0%)] compared to nulliparous. Similarly, younger women (<40 years of age) were significantly less likely to experience prolonged treatment duration [RFD (95% CI): -5.6% (-11.1%, -0.0%)] and more likely to undergo mastectomy [RFD (95% CI): 10.6% (5.2%, 16.0%)] compared to older women (≥40 years of age).

Conclusion: These results suggest that recently postpartum and younger women often received prompt and aggressive breast cancer treatment. Higher mortality and recurrence among recently pregnant women are unlikely to be related to undertreatment.

KEYWORDS:

Breast cancer; premenopausal women; treatment initiation delay; prolonged treatment duration; treatment modalities

DECLARATIONS

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Availability of data and material: For participant confidentiality and due to ethical restrictions, data are available upon request and are subject to data use agreements and other stipulations. Permission to access data from the Carolina Breast Cancer Study may be obtained online (https://unclineberger.org/cbcs/) or by contacting the authors.

Code availability: Not applicable.

Authors' contributions: Sanah N. Vohra – conceptualization, data curation, formal analysis, investigation, methodology, writing–original draft, and writing–review and editing. **Katherine E. Reeder-Hayes** – conceptualization, investigation, methodology, writing–original draft, and writing–review and editing. **Hazel B. Nichols** – conceptualization, investigation, methodology, writing–original draft, and writing–review and editing. **Marc A. Emerson** – conceptualization,

data curation, and writing–review and editing. **Michael I. Love** – conceptualization, investigation, methodology, writing–original draft, and writing–review and editing. **Andrew F. Olshan** – conceptualization, investigation, methodology, writing–original draft, and writing–review and editing. **Melissa A. Troester** – conceptualization, funding acquisition, project administration, investigation, formal analysis, methodology, writing–original draft, and writing–review and editing.

Ethics approval: All study protocols were approved by the Office of Human Research Ethics, Institutional Review Board at the University of North Carolina at Chapel Hill (UNC).

Consent to participate: Written informed consent was obtained from all individual participants included in the study prior to data collection.

Consent for publication: All participants consented to the submission of study results for journal publication.

Background (Limit: 3500 words; current: 2072 words)

Younger (<40 years of age) and recently postpartum (within 5 years of cancer diagnosis) women have been found to have worse breast cancer outcomes and higher mortality compared to other women with breast cancer [1-23]. Previous studies have hypothesized that tumor biology, delayed diagnosis, or treatment delay and variation contribute to poorer disease outcomes for recently postpartum women [1-7, 24-41]. Our recent findings, in the Carolina Breast Cancer Study (CBCS), suggest that breast tumors of recently postpartum women were more frequently node positive and had unique immune microenvironments, but it is unknown how common treatment delay is among these women. Previous analyses from the CBCS indicated that younger (<50 years of age) women had fewer treatment delays compared to older (50-74 years of age) women [42, 43], but comparisons in that study were not restricted to premenopausal women or to those with recent pregnancy. It is important to understand differences in treatment patterns for women with higher risk of aggressive cancers because delays and undertreatment are linked to worse overall and breast cancer-specific survival [44].

Using data from participants diagnosed with premenopausal breast cancers in CBCS Phase III, we hypothesized that stage at diagnosis, treatment initiation delay, prolonged treatment duration, and treatment modality would vary according to time since last childbirth and age at diagnosis. Recently postpartum women were defined as those diagnosed up to 5 years after their last full-term (≥7 months) pregnancy. Young-onset breast cancers were defined as cancers diagnosed at <40 years of age.

Methods

Study population

The CBCS phase III is a population-based study of women diagnosed with breast cancer in 44 counties of central and eastern North Carolina (2008-2013, N=2998); study details have been described previously [45-48]. Written informed consent was obtained at baseline prior to data collection. All study protocols were approved by the Office of Human Research Ethics, Institutional Review Board at the University of North Carolina at Chapel Hill (UNC). Briefly, the primary study enrolled 20–74-year-old women with first primary invasive breast cancer and oversampled for black and younger women (< 50 years of age) using randomized recruitment. The current analysis examined treatment time-related factors and treatment modality for premenopausal women under 50 years of age (N=1179). Only participants with stage I-III breast cancers were included, as treatment pathways for metastatic disease are distinct from those for localized disease. Additionally, we excluded participants who did not elect surgical treatment (N=5). Cases with missing data for last full-term birth were excluded (N=2). Breast cancers diagnosed during pregnancy were excluded (N=7). Figure 1 depicts participant numbers according to inclusion/exclusion criteria.

Recency of last childbirth

In-person interviews were conducted by trained nurses to collect medical history including detailed information on pregnancy history. Date of breast cancer diagnosis was collected by medical record abstraction. Time since last full-term birth was calculated by subtracting date of last full-term (≥7 months pregnancy) birth from date of breast cancer diagnosis. Women were grouped according to their time since last full-term birth: 0-5 years postpartum (N=160); 5.1-10 years postpartum (N=207); 10.1-20 years postpartum (N=438); 20.1-30 years postpartum (N=164). Women who never had a full-term (≥7 months) pregnancy prior to their diagnosis were assigned to the “nulliparous” group (N=210). Women who were up

to 5 years postpartum were referred to as recently postpartum. Women who were 10.1-20 years postpartum were referred to as remotely postpartum.

Treatment initiation, treatment modalities and prolonged treatment duration

Time to treatment initiation (in days) was defined as the time between breast cancer diagnosis and first treatment (defined as surgery, adjuvant or neoadjuvant chemotherapy, or radiation); this information was abstracted from medical records. Treatment initiation was categorized as occurring ≤ 30 vs. > 30 days after diagnosis, based on a recent publication by Bleicher et al. that reported better overall-survival among invasive non-metastatic breast cancer patients who received treatment within 30 days of diagnosis compared to longer wait to treatment initiation [49]. Information on treatment type, including type of surgery (mastectomy vs. breast-conserving surgery), chemotherapy receipt (yes vs. no), radiation therapy receipt (yes vs. no), and hormone therapy (yes vs. no), was abstracted from medical records. Participants were sorted in four treatment groups: surgery only, surgery and radiation, surgery and chemotherapy, and surgery, chemotherapy and radiation. Treatment duration was categorized within each treatment group by subtracting the date of last treatment from date of first treatment. Prolonged treatment duration (yes vs. no) was defined using American Cancer Society [50, 51] treatment recommendations within strata of treatment modality as follows: (1) surgery only, prolonged treatment duration was "yes" if surgery was performed ≥ 30 days after diagnosis, in-line with treatment initiation delay; (2) surgery and radiation, prolonged treatment duration was "yes" if treatment duration > 2 months [51]; (3) surgery and chemotherapy, prolonged treatment duration was " yes" if treatment duration > 6 months [50]; (4) surgery, radiation and chemotherapy, prolonged treatment duration was "yes" if treatment duration > 8 months [50, 51]. Information on breast cancer stage at diagnosis was abstracted from medical records.

Covariate assessment

Race was determined by self-report and categorized as Black or non-Black. Less than 2% of non-Black participants self-identified as multiracial, Hispanic, or other race/ethnicities. Age at diagnosis was obtained from the baseline survey and used as a continuous variable in models. Information on parity was obtained from baseline survey and categories as nulliparous, or 1, 2 and ≥ 3 full-term (≥7 months pregnancy) births. Self-reported income (USD < $20K, $20K-$50K, and >$50K), education (≤ high school education/GED, some college education/college degree, and post-graduate/professional degree), marital status (married vs. not married), and health insurance status (yes vs. no) were obtained from the baseline survey.

Statistical analyses

Descriptive statistics for patient sociodemographic and tumor characteristics of recently postpartum (0-5 years postpartum) and 5.1-10 years postpartum women were compared with nulliparous or remotely postpartum (10.1-20 years postpartum) women using chi-square tests or Fisher's exact tests when cell count <5. Generalized linear models were used to estimate relative frequency differences (RFDs) and 95% CIs as a measure of association for recency of last childbirth and age at diagnosis with respect to treatment initiation delay, prolonged treatment duration, and treatment modalities (type of surgery, chemotherapy receipt, radiation therapy receipt and hormone therapy receipt) [52]. Models were adjusted for age, race, tumor stage, size, grade, lymph node status, hormone receptor status and human epidermal growth factor receptor 2 status. Due to the limited cell size for recently (0-5 years) postpartum women without chemotherapy (n=20) and hormone therapy (n=14) treatment groups, these models were only adjusted for age and race. We minimally adjusted stage models for age, race, income, education, marital status, and health insurance status at baseline. All analyses were conducted in SAS

version 9.4 (SAS Institute, Cary, NC). P-values were two-sided with an alpha of 0.05 for statistical significance.

Results

Patient and Tumor characteristics

Among women with premenopausal breast cancer, 160 women were recently postpartum (0-5 years postpartum), 207 women were 5.1-10 years postpartum, 438 women were remotely postpartum (10.1-20 years postpartum), 164 women were 20.1-30 years postpartum women, and 210 women were nulliparous. Table 1 shows the distribution of age at diagnosis, race, parity, income, education, marital status, and health insurance at baseline according to time intervals from most recent childbirth. Recently postpartum women had a significantly younger age at diagnosis (median = 37 years) compared to those who were remotely postpartum (median = 44 years) or were nulliparous (median = 42 years). Although no significant difference in race was observed between recently postpartum and nulliparous group, the 20.1-30 years postpartum group had a higher frequency of Black compared to non-Black participants, consistent with a trend toward younger age at first birth among Black women in this study population. Recently postpartum women were significantly more likely to have health insurance at baseline (94.4% vs. 88.6%) and were more commonly married (73.1% vs. 40.0%) compared to nulliparous women. Compared to remotely postpartum women, recently postpartum women had higher income and education, and were more likely to be primiparous. There were no differences in income and education between recently postpartum and nulliparous women.

Tumor stage at diagnosis & Treatment time-related factors

Recently postpartum women were significantly more likely to have stage III disease [RFD (95% CI): 12.2% (3.6%, 20.8%)] compared to nulliparous women, and these differences

remained significant even after adjustment for age, race and socioeconomic factors including income, education, health insurance status and marital status. The median time to treatment initiation was 31 days (interquartile range, 20-44). Approximately 60% of participants had treatment initiation > 30 days after diagnosis. After adjustment for age, race and standard clinical tumor characteristics, recently postpartum women were significantly less likely to have delayed treatment initiation and prolonged treatment duration compared to nulliparous women and compared to remotely postpartum (Table 2 & Figure 2). Similarly, younger women (<40 years) were significantly less likely to experience prolonged treatment duration compared to older women (≥40 years), but no significant difference was observed with respect to tumor stage and delayed treatment initiation (Table 3 & Figure 3).

Treatment modalities

Recently postpartum women were more likely to receive more aggressive treatments compared to nulliparous women (Table 4). Considering type of surgery, the relative frequency difference for recency of birth was attenuated after adjusting for age, race, and standard clinical tumor characteristics, but women who were up to 10 years postpartum remained significantly more likely to get mastectomy (vs. breast-conserving surgery) compared to nulliparous women. Considering chemotherapy, associations with recency of birth were strongly related to tumor stage; we were unable to adjust for clinical tumor characteristics due to positivity violations, with all stage III cases in the recently pregnant group receiving chemotherapy. Thus, the association between postpartum status and chemotherapy is not independent of tumor characteristics. With respect to radiation therapy and hormone therapy (among ER positive and borderline cases only), no significant differences were observed between the recently postpartum and nulliparous group. Similarly, treatment patterns among younger vs. older women were strongly related to tumor

clinical characteristics (especially, stage at diagnosis and lymph node status), with younger women being significantly more likely to received mastectomy, chemotherapy and less likely to receive radiation and hormone therapy compared to older women (Table 3 & Figure 3). Finally, sensitivity analyses conducted including cases diagnosed during pregnancy (n=7) in the recently postpartum group (n=160) did not alter these results.

Discussion

In the Carolina Breast Cancer Study Phase III, conducted between 2008-2013, recently postpartum women had prompt and aggressive post-diagnostic treatment, at least in part due to more aggressive clinical tumor characteristics (i.e., later stage and lymph node positivity). Recently pregnant women tended to have later stage at diagnosis, prompt treatment initiation, shorter treatment duration, and were more likely to receive mastectomy (vs. breast-conserving surgery) and chemotherapy. These trends were mirrored by patterns in young-onset (<40 years of age) breast cancer cases. These findings suggest that patterns of poorer outcomes for recently pregnant and younger women are not driven by undertreatment or treatment delays.

Only one previous study has examined treatment initiation delay with respect to recency of pregnancy; however, that study compared pregnant vs. postpartum breast cancer cases and reported delayed initiation among pregnant women [3]. No previous studies have evaluated treatment timelines among postpartum women or comparing postpartum women to nulliparous women. Similarly, few studies have investigated treatment modality among recently pregnant women [1-4]. The majority of these studies found no significant association between treatment modality such as receipt of chemotherapy [1-3], radiation [1, 4] and surgery [1-4], and recency of pregnancy. However, previous studies included pregnant women[53, 54], for whom treatment plans must address risk to both mother and child, and therefore are difficult to interpret relative

to our analysis of premenopausal breast cancer among postpartum and nulliparous women. The current findings separating the postpartum period add resolution to the unique experience of this group.

Recent pregnancy and younger age both were associated with treatment timeliness and modality, but the higher incidence of more aggressive tumors appeared to drive the shift in treatment patterns for both groups. We were not able to examine these relationships separately by race due to limited number of recently postpartum cases. We were also not able to evaluate differences in specific chemotherapy regimens. Future research should address whether social support, childcare needs, or other treatment-related "workload" experiences by younger women influence their reported quality of life and stress levels. Our results show that worse breast cancer outcomes among younger and recently postpartum women are unlikely to be related to post-diagnostic undertreatment.

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Figure 1: Study population inclusion/exclusion criteria flowchart

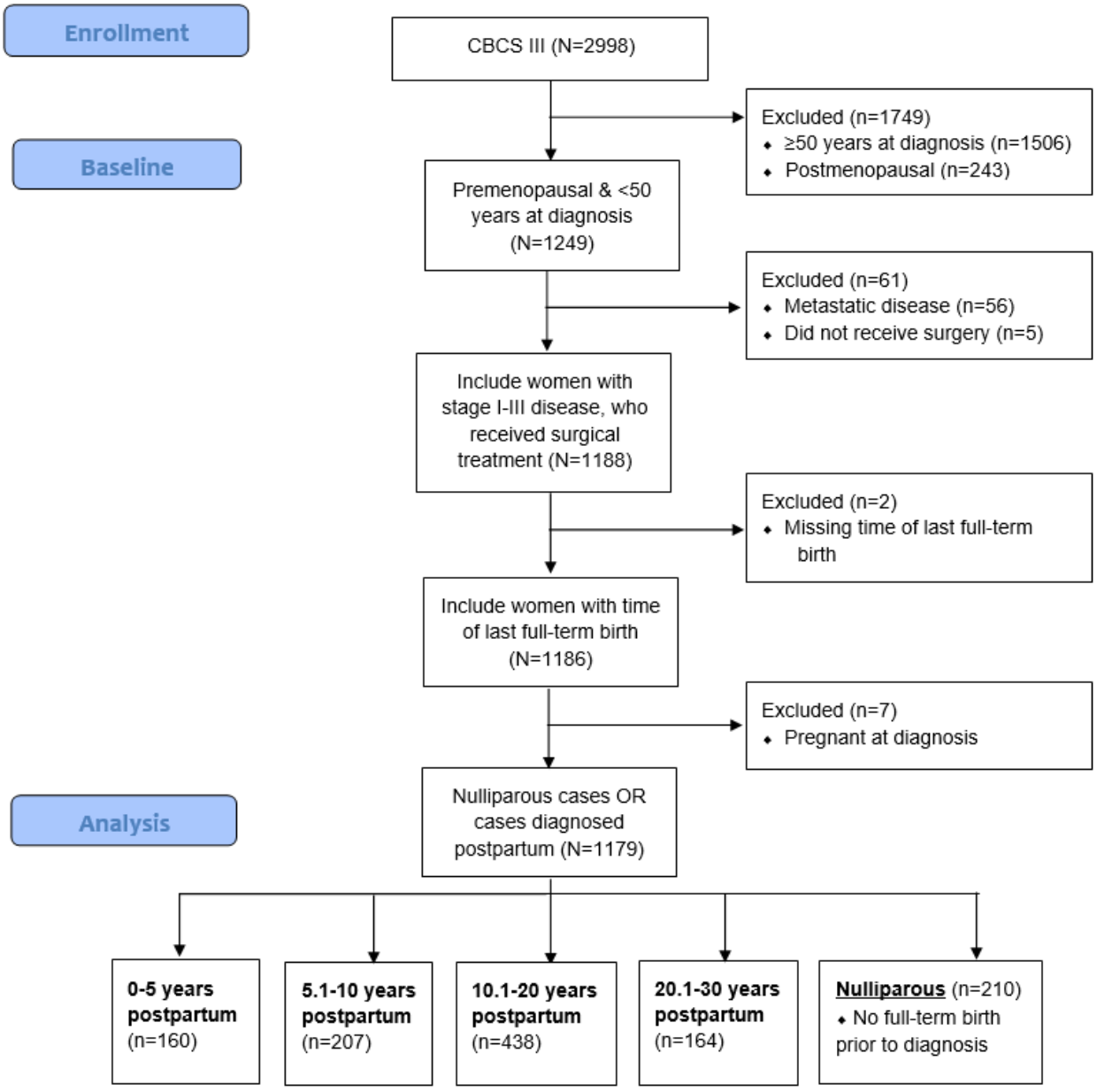


Table 1: Distribution of select characteristics by time since last childbirth among premenopausal women <50 years of age in Carolina Breast Cancer Study - Phase III, 2008-2013 (N=1179)

		Nulliparous (N=210)	0-5 postpartum (N=160)	5.1-10 postpartum (N=207)	10.1-20 postpartum (N=438)	20.1-30 postpartum (N=164)
Age at diagnosis (years)						
Median (Range)		42 (23, 49)	37 (24, 49)	41 (26, 49)	44 (30, 49)	47 (38, 49)
	<30	14 (6.7)	17 (10.6)	4 (1.9)	0 (0.0)	0 (0.0)
	30-39	52 (24.8)	96 (60.0)	78 (37.7)	60 (13.7)	1 (0.61)
	40-49	144 (68.6)	47 (29.4)	125 (60.4)	378 (86.3)	163 (99.4)
	p-value [a]	<0.0001				
Race						
	Black	97 (46.2)	77 (48.1)	92 (44.4)	209 (47.7)	108 (65.9)
	Non-Black	113 (53.8)	83 (51.9)	115 (55.6)	229 (52.3)	56 (34.2)
	p-value [a]	0.7				
Parity						
	1	-	47 (29.4)	47 (22.7)	94 (21.5)	64 (39.0)
	2	-	57 (35.6)	86 (41.6)	199 (45.4)	61 (37.2)
	≥3	-	56 (35.0)	74 (35.8)	145 (33.1)	39 (23.8)
	p-value [b]		0.05			
Income						
	<$20,000	34 (16.8)	19 (12.0)	24 (11.9)	80 (19.1)	46 (29.3)
	$20,000-50,000	64 (31.5)	44 (27.9)	52 (25.7)	134 (32.0)	47 (29.9)
	>$50,000	105 (51.7)	95 (60.1)	126 (62.4)	205 (48.9)	64 (40.8)
	p-value [a]	0.2				

Education					
≤High school graduate/GED	45 (21.4)	26 (16.2)	50 (24.1)	140 (32.0)	81 (49.4)
Some college/College graduate	121 (57.6)	99 (61.9)	119 (57.5)	249 (57.0)	80 (48.8)
Post-graduate/Professional degree	44 (21.0)	35 (21.9)	38 (18.4)	48 (11.0)	3 (1.8)
p-value [a]	0.5				
Married					
No	126 (60.0)	43 (26.9)	63 (30.4)	164 (37.5)	72 (43.9)
Yes	84 (40.0)	117 (73.1)	144 (69.6)	273 (62.5)	92 (56.1)
p-value [a]	<0.0001				
Health Insurance at Baseline					
Yes	186 (88.6)	151 (94.4)	198 (96.1)	412 (94.3)	150 (91.5)
No	24 (11.4)	9 (5.6)	8 (3.9)	25 (5.7)	14 (8.5)
p-value [a]	0.05				

[a] P-values generated by chi-square test between nulliparous and >0-5 years postpartum women, except when expected cell count <5, they were calculated by Fisher's exact test. [b] P-value for chi-square test between women >0-5 years vs. >10-20 years postpartum. Missing values were excluded from percentage calculations. Percentages may not add up to 100 due to rounding.

Table 2: Association between breast cancer tumor stage & treatment time-related factors and recency of last childbirth among premenopausal women <50 years of age in the Carolina Breast Cancer Study, 2008-2013 (N=1179)

	Nulliparous (N=210)	0-5 postpartum (N=160)	5.1-10 postpartum (N=207)	10.1-20 postpartum (N=438)	20.1-30 postpartum (N=164)
Stage					
I-II	181 (86.2)	119 (74.4)	175 (84.5)	365 (83.3)	135 (82.3)
III	29 (13.8)	41 (25.6)	32 (15.5)	73 (16.7)	29 (17.7)
III vs. I-II, Age & Race-Adjusted RFD (95% CI)	Ref.	12.6% (4.0%, 21.1%)	2.6% (-4.2%, 9.3%)	3.4% (-2.4%, 9.1%)	2.8% (-4.7%, 10.4%)
Fully Adjusted RFD (95% CI) [a]	Ref.	12.2% (3.6%, 20.8%)	1.8% (-4.8%, 8.5%)	2.3% (-3.5%, 8.1%)	1.1% (-6.5%, 8.7%)
Delayed Initiation					
≤30 days	122 (58.1)	115 (71.9)	130 (62.8)	284 (64.8)	91 (55.5)
>30 days	88 (41.9)	45 (28.1)	77 (37.2)	154 (35.2)	73 (44.5)
>30 vs. ≤30 days, Age & Race-Adjusted RFD (95% CI)	Ref.	-14.6% (-25.1%, -4.2%)	-5.0% (-14.8%, 4.8%)	-8.4% (-16.9%, 0.1%)	-0.2% (-11.2%, 10.9%)
Fully Adjusted RFD (95% CI) [b]	Ref.	-11.2% (-21.4%, -1.0%)	-3.2% (-13.0%, 6.5%)	-7.1% (-15.4%, 1.3%)	1.0% (-10.2%, 12.1%)
Prolonged Treatment Duration					
No	113 (53.8)	112 (70.0)	104 (50.2)	259 (59.1)	88 (53.7)
Yes	97 (46.2)	48 (30.0)	103 (49.8)	179 (40.9)	76 (46.3)
Yes vs. No, Age & Race-Adjusted RFD (95% CI)	Ref.	-17.2% (-27.8%, -6.6%)	4.8% (-5.3%, 14.8%)	-6.0% (-14.7%, 2.6%)	-3.1% (-14.1%, 7.9%)

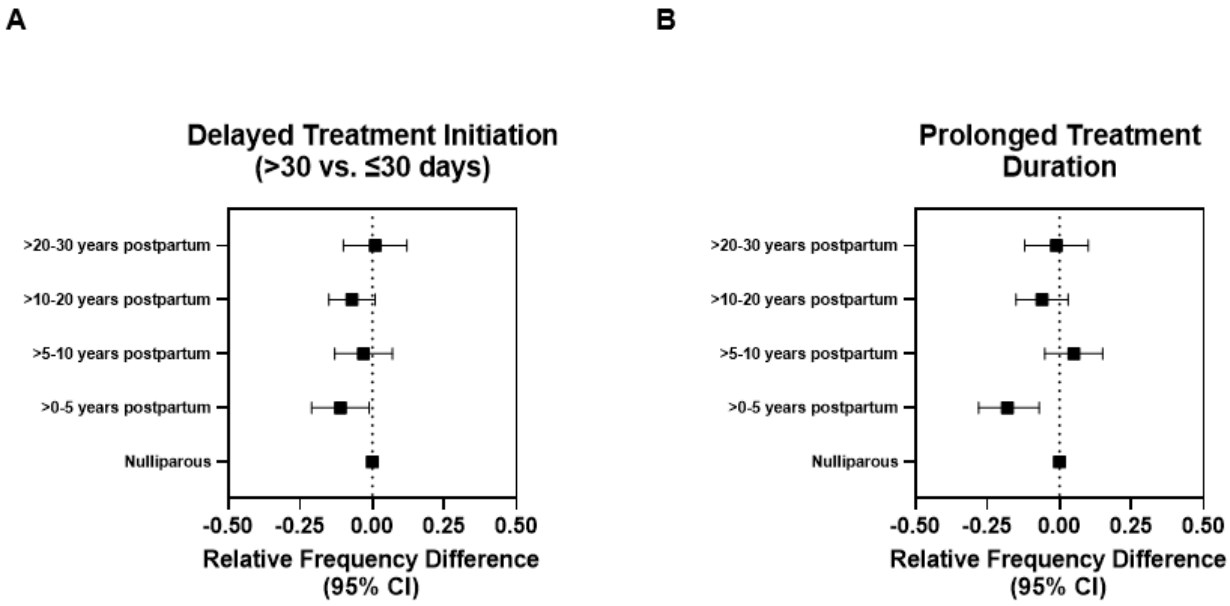
Fully Adjusted RFD (95% CI) [b]	Ref.	-17.5% (-28.0%, -7.1%)	4.6% (-5.4%, 14.6%)	-5.8% (-14.5%, 2.8%)	-1.1% (-12.3%, 10.1%)

Abbreviations: RFD, relative frequency difference; CI, confidence interval

[a] Adjusted for age, race, income, education, marital status, and health insurance status at baseline

[b] Adjusted for age, race, tumor stage, size, grade, lymph node status, hormone receptor status and human epidermal growth factor receptor 2 status

Figure 2: Association between treatment timing and recency of last childbirth



(A & B) Forest plots of relative frequency difference for treatment time-related factors by time since last childbirth, adjusted for age, race, tumor stage, size, grade, lymph node status, hormone receptor status and human epidermal growth factor receptor 2 status. CI: confidence interval.

Table 3: Association between breast cancer stage at diagnosis & treatment-related factors and young age at diagnosis in the Carolina Breast Cancer Study, 2008-2013 (N=2842)

	Young (N=351)	Old (N=2491)	Young vs. Old Race-Adjusted RFD (95% CI)	Young vs. Old Model 1* RFD (95% CI)	Young vs. Old Full Model [a] RFD (95% CI)
Stage [b]					
I-II	285 (81.2)	2134 (85.7)	Ref.	-	Ref.
III	66 (18.8)	357 (14.3)	3.5% (-1.0%, 7.9%)	-	3.5% (-1.1%, 8.1%)
Delayed Initiation					
≤30 days	232 (66.1)	1615 (64.8)	Ref.	Ref.	Ref.
>30 days	119 (33.9)	876 (35.2)	-1.2% (-6.7%, 4.3%)	-2.0% (-7.5%, 3.6%)	-1.2% (-6.8%, 4.3%)
Prolonged Treatment Duration					
No	216 (61.5)	1306 (52.4)	Ref.	Ref.	Ref.
Yes	135 (38.5)	1185 (47.6)	-8.9% (-14.6%, -3.3%)	-7.7% (-13.3%, -2.0%)	-5.6% (-11.1%, -0.0%)
Type of Surgery					
Mastectomy	204 (58.3)	1077 (43.2)	15.1% (9.4%, 20.8%)	10.7% (5.3%, 16.2%)	10.6% (5.2%, 16.0%)
Breast-conserving surgery	146 (41.7)	1414 (56.8)	Ref.	Ref.	Ref.
Received Chemotherapy [c]					
Yes	299 (85.2)	1516 (60.9)	22.2% (18.2%, 26.2%)	9.1% (6.6%, 11.6%)	-
No	52 (14.8)	975 (39.1)	Ref.	Ref.	-
Received Radiation					

	Yes	241 (68.7)	1835 (73.7)	-4.7% (-9.9%, 0.6%)	-5.2% (-10.4%, 0.0%)	-6.0% (-11.2%, -0.8%)
	No	110 (31.3)	656 (26.3)	Ref.	Ref.	Ref.
Received Hormone therapy [c, Φ]						
	Yes	194 (85.1)	1672 (90.4)	-5.4% (-10.4%, -0.4%)	-5.9% (-10.9%, -0.9%)	-
	No	34 (14.9)	178 (9.6)	Ref.	Ref.	-

Abbreviations: RFD, relative frequency difference; CI, confidence interval

* Model 1 – Adjusted for race, tumor stage, and lymph node status

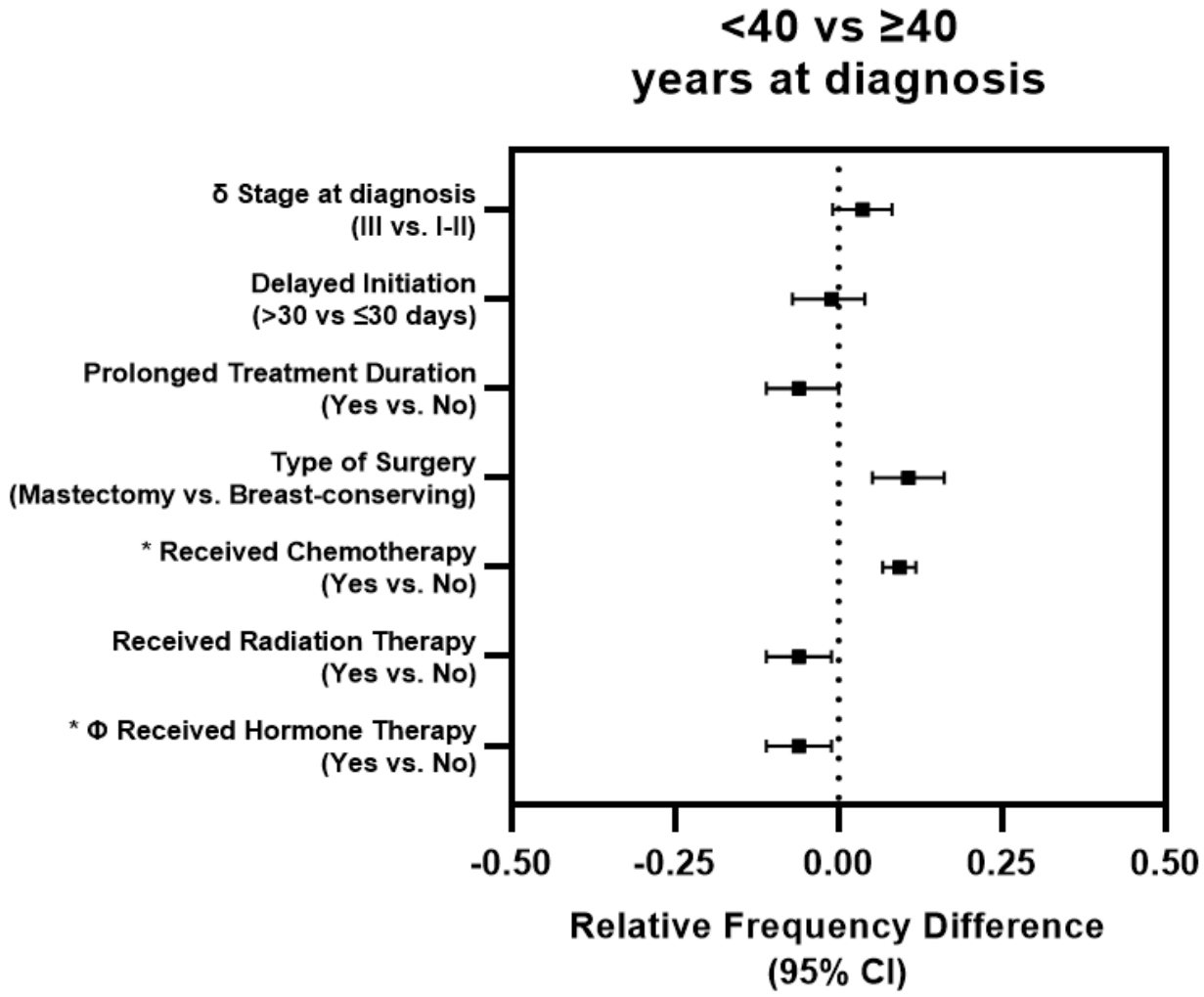
[a] Full Model – Adjusted for race, tumor stage, size, grade, lymph node status, hormone receptor status and human epidermal growth factor receptor 2 status

[b] Full Model for Stage – Adjusted for race, income, education, marital status, and health insurance status at baseline

[c] Fully Adjusted model not possible due to limited cell size

[Φ] Includes only ER positive and borderline cases (≥1% cell positivity)

Figure 3: Associations between tumor stage at diagnosis & treatment-related factors and young age at diagnosis



Forest plot of relative frequency difference for tumor stage at diagnosis, treatment time-related factors and treatment received between cases diagnosed at <40 vs. ≥40 years of age. **δ** Stage model adjusted for age, race, income, education, marital status and health insurance status at baseline. Treatment time-related factors and treatment received adjusted for race, tumor stage, size, grade, lymph node status, hormone receptor status and human epidermal growth factor receptor 2 status; * only adjusted for race, tumor stage and lymph node status due to small number of untreated cases. Φ Includes only ER positive and borderline cases (≥1% cell positivity). CI: confidence interval.

Table 4: Distribution of treatment received and recency of last childbirth among premenopausal women <50 years of age in the Carolina Breast Cancer Study, 2008-2013 (N=1179)

	Nulliparous (N=210)	0-5 postpartum (N=160)	5.1-10 postpartum (N=207)	10.1-20 postpartum (N=438)	20.1-30 postpartum (N=164)
Type of Surgery					
Mastectomy	99 (47.1)	106 (66.7)	127 (61.4)	219 (50.0)	83 (50.6)
Breast-conserving surgery	111 (52.9)	53 (33.3)	80 (38.6)	219 (50.0)	81 (49.4)
Mastectomy vs. Breast-conserving surgery, Age & Race-Adjusted RFD (95% CI)	Ref.	18.2% (7.5%, 29.0%)	14.3% (4.5%, 24.1%)	4.5% (-4.1%, 13.1%)	8.8% (-2.1%, 19.7%)
Fully Adjusted RFD (95% CI) [a]	Ref.	14.9% (4.8%, 25.0%)	15.0% (5.4%, 24.5%)	4.1% (-4.4%, 12.5%)	9.8% (-1.0%, 20.6%)
Received Chemotherapy					
Yes	147 (70.0)	140 (87.5)	145 (70.0)	333 (76.0)	129 (78.7)
No	63 (30.0)	20 (12.5)	62 (30.0)	105 (24.0)	35 (21.3)
Yes vs. No, Age & Race-Adjusted RFD (95% CI)	Ref.	10.1% (1.0%, 19.3%)	0.1% (-9.1%, 9.3%)	6.4% (-1.3%, 14.1%)	9.3% (-0.2%, 18.9%)
Received Radiation					
Yes	146 (69.5)	110 (68.8)	137 (66.2)	327 (74.7)	118 (72.0)
No	64 (30.5)	50 (31.2)	70 (33.8)	111 (25.3)	46 (28.0)
Yes vs. No, Age & Race-Adjusted RFD (95% CI)	Ref.	-1.5% (-11.4%, 8.3%)	-2.9% (-12.1%, 6.3%)	2.8% (-4.7%, 10.4%)	-2.5% (-12.3%, 7.2%)
Fully Adjusted RFD (95% CI) [a]	Ref.	-3.4% (-13.6%, 6.8%)	-4.9% (-13.4%, 3.7%)	-0.9% (-8.0%, 6.3%)	-5.8% (-14.8%, 3.1%)

Received Hormone therapy [Φ]					
Yes	143(87.2)	94 (87.0)	138 (89.0)	279 (87.7)	84 (87.5)
No	21 (12.8)	14 (13.0)	17 (11.0)	39 (12.3)	12 (12.5)
Yes vs. No, Age & Race-Adjusted RFD (95% CI)	Ref.	1.6% (-6.4%, 9.6%)	3.3% (-3.8%, 10.4%)	1.2% (-4.9%, 7.4%)	1.3% (-7.2%, 9.7%)

Abbreviations: RFD, relative frequency difference; CI, confidence interval

[a] Adjusted for age, race, tumor stage, size, grade, lymph node status, hormone receptor status and human epidermal growth factor receptor 2 status

[Φ] Includes only ER positive and borderline cases (≥1% cell positivity)